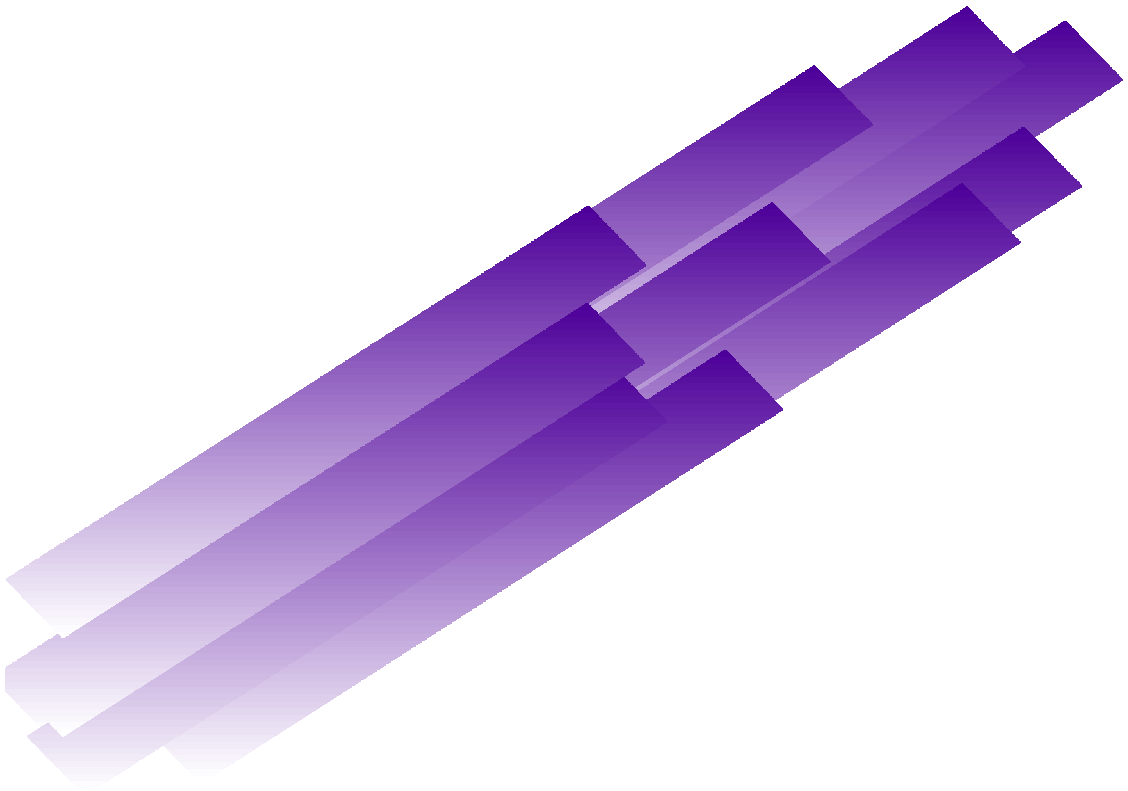
Guidance for Industry

Current Good Manufacturing Practices For Positron Emission Tomographic (PET) Drug Products



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
April 1997

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The Drug Information Branch
Division of Communications Management, CDER, FDA, HFD-210
5600 Fishers Lane, Rockville MD 20857
(Tel) 301-827-4573
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GUIDANCE FOR INDUSTRY[1]

CURRENT GOOD MANUFACTURING PRACTICES FOR POSITRON EMISSION TOMOGRAPHIC (PET) DRUG PRODUCTS

I. INTRODUCTION

This guidance document provides information on certain practices, procedures, and facilities used to manufacture positron emission tomographic (PET) radiopharmaceutical drug products. The primary focus is on current good manufacturing practice (CGMP) requirements that may cause particular concern due to the special characteristics inherent in the production and control of PET radiopharmaceutical drug products.

It is essential that all drug manufacturing comply with CGMP regulations for finished pharmaceuticals [21 CFR Parts 210 and 211]. Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) deems a drug to be adulterated if the methods used in, or the facilities or controls used for, its manufacturing, processing, packing, or holding do not conform to, or are not operated or administered in conformity with current good manufacturing practice to ensure that such drug meets the requirements of the Act as to safety, has the identity and strength, and meets the quality and purity characteristics it purports or is represented to possess.

This guidance describes some of the manufacturing operations and controls used to prepare PET radiopharmaceutical drug products. Compared with conventional drug product manufacture, the manufacture of PET radiopharmaceutical drug products presents unique regulatory concerns including, but not limited to the following:

- The short physical half-life of positron emitting radionuclides. Generally, no more than two or three half-lives should elapse between the end of radionuclide production and the completion of drug manufacture.

- The scale of manufacturing that typically parallels the demand of a relatively small number of patients. Manufacturing may be limited to only one or a few lots produced

[1]This guidance has been prepared by the Office of Compliance (HFD-300) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the manufacture of positron emission tomographic (PET) radiopharmaceutical drug products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

each day with a lot being as small as one vial.

- The need to administer PET radiopharmaceutical drug products to patients within a short period of time after manufacturing because of the short physical half-lives of these products.

FDA has proposed amending its regulations to permit manufacturers of PET radiopharmaceutical drug products to petition FDA for exceptions or alternatives to provisions of the CGMP regulations (60 FR 10517). FDA expects to finalize the amended regulations soon. Under the revised regulations, FDA may approve a request for an exception or alternative that meets certain requirements. FDA's actions are intended to relieve manufacturers of PET radiopharmaceutical drug products from regulations that (1) might result in unsafe handling of these products, (2) are inapplicable or inappropriate, and (3) do not enhance safety or quality in the manufacture of PET radiopharmaceutical drug products. The Agency may approve a request for an exception or alternative if: (1) The requestor's compliance with the CGMP requirement is unnecessary to ensure that the drug meets the safety requirements of the act and has the identity, strength, quality, and purity characteristics it purports to possess; (2) compliance with the requirement cannot be achieved; (3) the requestor's alternative procedures or controls satisfy the purpose of the requirement; or (4) the requestor's submission otherwise justifies an exception or alternative.

To maintain a publicly available record of requests for exceptions and alternatives and Agency action on such requests, FDA has decided that requests for exceptions and alternatives should be submitted in the form of a citizen petition under 21 CFR 10.30. A request for an exception or alternative should be clearly identified as a PET Request for Exception or Alternative to the CGMP Regulations. A citizen petition requesting an exception or alternative should contain one or more of the following: (1) An explanation, with supporting data as necessary, of why compliance with a particular requirement of the CGMP regulations is unnecessary or cannot be achieved; (2) a description, with supporting data as necessary, of alternate procedures or controls that satisfy the purpose of the CGMP requirement; or (3) other information justifying an exception or alternative. These three options will provide PET manufacturers the opportunity to present a variety of data and other information to support an exception or alternative.

This guidance does not attempt to address all sections of the CGMP regulations that might apply to PET radiopharmaceuticals. Radiation safety requirements and dispensing or administration of patient doses are not covered in this guidance. This guidance does not in any way affect the ability of the Agency to establish specific requirements or standards regarding PET radiopharmaceutical drug products within the context of new drug application reviews. Likewise, this document is not intended to address specific issues related to such applications.

This guidance supersedes the "Guide to Inspections of Liquid Injectable Radiopharmaceuticals Used in Positron Emission Tomography (PET)," November 1993.

II. QUALITY CONTROL UNIT

A. Regulatory Requirements

A *quality control unit* is any person or an organizational element designated by the firm to be responsible for the duties related to quality control [21 CFR 210.3(b)(15)]. The quality control unit has responsibility and authority for certain actions [21 CFR 211.22]:

1. Approving or rejecting components, containers, and closures [21 CFR 211.84], in-process materials [21 CFR 211.110], and quarantined finished products [21 CFR 211.142 and 211.165].

2. Reviewing and approving or rejecting written documents and records, such as production and control procedures and specifications [21 CFR 211.100], and production and control records [21 CFR 211.192], ensuring that no manufacturing deviations (errors) have occurred.

3. Fully investigating manufacturing deviations, if they occur [21 CFR 211.192].

4. Maintaining complaint files involving the possible failure to meet predetermined drug product specifications [21 CFR 211.198].

B. Guidance

Some quality control units in some PET centers may consist of just a single person, provided the center's workload is sufficiently low to justify such staffing levels. In other situations, employees who are not directly related to PET production and who are fully trained and qualified may perform functions in the quality control unit.

In some limited, justified situations, individuals may be simultaneously responsible for both quality control and production functions. Outside consultants with appropriate qualifications may perform one or more of the functions of the quality control unit [21 CFR 211.34]. Where a single person is ultimately responsible for both the quality control unit and production, an outside consultant should perform at least some of the quality control unit functions. Such delegated functions could include the review and approval of written documents, procedures, and specifications.

Regardless of the staffing levels or pattern of personnel assignment, the quality control unit should have the necessary authority to ensure that the functions of the unit are both

fully and objectively achieved. The unit's authority and responsibility should not be subordinated to any other unit. The unit should maintain autonomy in rendering and implementing the decisions necessary to ensure adequate process control and the quality of released products. For example, once decisions are made by the quality control unit to reject lots, such decisions should not be subject to further review or revocation by another organizational component or person. Written procedures should be established to ensure that the responsibilities listed above are fulfilled.

III. PERSONNEL QUALIFICATIONS

A. Regulatory Requirements

Appropriate and adequate training of personnel is required in 21 CFR 211.25. According to the regulation, a staff member must have the education, training, and experience, or combination thereof, to enable that person to perform his or her assigned functions. The regulation also requires that supervisors have appropriate knowledge and skills.

B. Guidance

FDA acknowledges that some PET centers may be operating with as few as one or two people to accomplish all production and control functions. Nevertheless, production and control personnel in all PET centers should have a broad range and level of appropriate formal education, training, and experience in the areas of radiopharmacy, radiochemistry, nuclear physics, manufacturing and testing of PET radiopharmaceuticals, as well as current good manufacturing practices.

All personnel performing aseptic processes should be thoroughly trained in these techniques and in maintaining aseptic environmental quality. This training should be in addition to that necessary to properly manufacture PET radiopharmaceutical drug products. All training should be appropriate to the scale and configuration of the aseptic operation in which personnel are working.

One example is the general principle of keeping gloved hands away from critical areas and surfaces while preserving the laminar airflow. Generally, different manipulative approaches are used depending upon whether the operation is manual or automated and whether it is performed under vertical or horizontal flow. All personnel entering a controlled area should be appropriately trained in procedures (e.g., gowning) used for maintaining adequate environmental controls in the PET center.

Because the maintenance of environmental quality and the prevention of product contamination are heavily dependent upon adequate personnel practices within all

controlled environments, personnel practices should be monitored. At established intervals, an experienced, knowledgable observer should objectively assess the aseptic technique and environmental control practices of all personnel. These evaluations also should include routine physical assessments of aseptic technique and environmental control practices, such as swab or touch plates testing. Personnel employing unapproved practices should be retrained and requalified before resuming procedures in the critical areas or before reentry into the controlled area is permitted.

FDA does not expect most PET centers with small staffs of scientific and professional personnel to have in-house training programs. However, all PET centers should have an appropriate, written plan that is followed closely to ensure that each staff member maintains current, necessary professional-scientific competency, including competency in current good manufacturing practices. This written plan may include programs from externally provided continuing education, training, or directed experience (in-house training programs).

IV. BUILDINGS, FACILITIES, AND PERSONNEL RESPONSIBILITIES

A. Regulatory Requirements

21 CFR 211.42 (design and construction) requires separate or defined areas of operation to prevent contamination and, in conjunction with aseptic processing, high-efficiency particulate air (HEPA) filtration, positive pressure, proper equipment maintenance to control aseptic conditions, and a system for monitoring environmental conditions.

21 CFR 211.46 (ventilation, air filtration, air heating and cooling) requires, in part, that equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature be provided where appropriate and that an air filtration system, including prefilters and high efficiency particulate air (HEPA) filters, be used when appropriate on air supplies to production areas.

21 CFR 211.28(a) requires that protective apparel be worn as necessary to protect drug products from contamination. 21 CFR 211.28(d) requires a person having any illness or open lesions that may adversely affect the safety or quality of drug products be excluded from direct production activities.

21 CFR 211.56 (sanitation) requires, in part, written procedures for clean and sanitary conditions in any building used for manufacture of drug products.

B. Facility Design and Function

The facility design for that part of the PET center where radiopharmaceutical drug products are manufactured should protect the product from possible contamination from personnel, equipment, and the surrounding environment.

NOTE: Facility design also should protect personnel from unnecessary radiation exposures and hazards. The principles of radiation protection and safety are not included as part of this CGMP guidance. Other regulatory guidance and sources should be consulted regarding this subject.

Environmental conditions can significantly contribute to potential microbial and particulate contamination of aseptically processed products. *Critical areas* are those in which the sterilized dosage forms, containers, and closures are exposed to the environment, particularly the environment immediately surrounding aseptic-processing activities and critical surfaces (a *critical surface* is any surface that comes into contact with a sterilized product, sterile containers, or sterile closures). FDA's "Guideline on Sterile Drug Products Produced by Aseptic Processing" (June 1987) provides further guidance on critical and controlled areas.

Strict control of the microbial and particulate loads in the critical areas and around critical surfaces is essential. PET centers should consistently maintain at least Class 100 conditions in the atmosphere immediately surrounding critical areas and surfaces during aseptic activities.

The microbial and particulate characteristics within the controlled area (Class 100,000) and within the buffering conditions (preferably maintained at Class 10,000) have direct effects on a PET center's ability to maintain the appropriate conditions in areas immediately surrounding critical areas and surfaces. It is essential to prevent microbial and particulate contamination of the manufacturing process and the final product.

All activities performed under aseptic techniques involving critical surfaces should be performed in critical areas that are maintained under at least Class 100 conditions. Critical activities in the manufacture of PET radiopharmaceuticals may include, but are not limited to:

1. Aseptic addition of a sterile diluent, such as sodium chloride 0.9% injection, to a sterile, stoppered vial using needle/syringe technique

2. Aseptic attachments of sterile components and devices

Examples of such activities include: connection of a sterile syringe or a sterile filter device to a sterile needle; insertion of a sterile needle through a sanitized stopper into a vial; and any penetration of, or creation of an open pathway into a sealed container-closure system after filling, as might occur with some

postfilling sampling techniques.

NOTE: If activities 1 and/or 2 are performed improperly, there is a potential for contamination of the sterile product or sterile product contact surface.

3. Allocation of a lot of an injectable PET radiopharmaceutical into unit-dose containers

To ensure that activities, such as aseptic tasks, are maintained within the designated criteria for critical areas and for critical surfaces, the Class 100 areas should be completely surrounded by buffering conditions, preferably maintained at least at Class 10,000 conditions. The buffering conditions, in turn, should be located within a controlled area maintained at least at Class 100,000 conditions.

C. Critical Areas and Surfaces (Class 100); Buffering Conditions (preferably Class 10,000)

As defined above, a critical area is one in which the sterilized dosage form, containers, and closures are exposed to the environment. Activities conducted in critical areas include any manipulations of sterilized materials or products prior to and during the filling or closing operations. These activities are conducted in what is typically known as the aseptic core or aseptic processing area.

A critical area (Class 100) is essential because the finished product is not processed further in its immediate container and is vulnerable to contamination. Therefore, to maintain the quality and, specifically, the sterility of the product, the environment in the immediate proximity of the actual operations should be of the highest quality.

One essential aspect of environmental quality is the particulate content of the air. Particles can enter a product and contaminate it physically or biologically by acting as a vehicle for microorganisms. It is important to minimize the particle content of the air and to effectively remove those particles that are present. Maintaining a minimum of Class 100,000 in the controlled area with buffering conditions, preferably at Class 10,000 conditions, provides an acceptably low risk of contaminants being blown, dragged, or otherwise introduced into the critical areas and critical surfaces from the surrounding atmosphere. Critical areas and critical surfaces should be fully enveloped with buffering conditions (preferably maintained at least at Class 10,000 conditions).

One potentially significant source of microbial and particulate contamination is room air. Air in critical areas should be supplied as HEPA filtered laminar flow air, having a velocity sufficient to sweep particulate matter away from the filling and closing area. Normally, a velocity of 90 feet per minute, plus or minus 20 percent, is adequate. However, higher velocities may be needed where operations generate high levels of

particles or where equipment configurations disrupt laminar flow. Measurements should be taken at the HEPA filter face and at the product filling heights to determine acceptability. Microbial contamination not exceeding one colony forming unit per 10 cubic feet is considered attainable and desirable.

Different areas in the manufacturing process should be separated by absolute physical barriers (e.g., solid panels) whenever possible and may be supplemented as necessary by partial physical barriers (e.g., air curtains) and procedural controls. In addition, the recommended use of minimum Class 100,000 controlled areas with buffering conditions (preferably at least Class 10,000) should be adequate to achieve and maintain conditions for performance of aseptic techniques within the designated Class 100 critical areas.

In meeting the requirements of 21 CFR 211.42, PET centers can perform aseptic techniques within suitable, effective critical areas located in a vertical or horizontal laminar airflow workbench (LAFW). Aseptic techniques within an LAFW may include relatively simple manipulations of commercially available, sterile, ready-to-use sealed devices, tubing and containers.

In using a vertical or horizontal LAFW, an acceptable separation between areas within the manufacturing facility could be achieved as follows:

1. Separating buffering conditions from the controlled area

    a. With vertical recirculating LAFWs

    The front panel is lowered to manufacturer specifications. A constant air barrier is provided below the panel, and the proper technique is used for the introduction of articles into the buffering conditions.

    b. With horizontal LAFWs (no front panel)

    Maintaining Class 100 conditions within the critical area is entirely dependent on the outflow of air moving horizontally across the critical area. Therefore, the entire opening to the critical area should be protected from gusts of air entering the buffering conditions from the controlled area. One solution could be to hang plastic sheeting in such a manner as to create an acceptable buffering condition surrounding the front of the horizontal LAFW's opening, effectively isolating the critical area from the controlled area. This plastic sheeting should extend several feet above the top of the LAFW work space, surround all three sides, and extend at least 12 inches below the level of the critical area. Overlapping panels of plastic sheeting, which would allow ready entry

and exit of personnel and goods, may be acceptable.

The appropriate distance between the edge of the critical area and the back plastic panel should be determined and established to maintained an adequate air flow. The distance should be adequate to ensure and prevent deviations in the rate of laminar air flow near the edge of the critical area. The proper distance should be confirmed by the combination of visual evaluation of air flow patterns (e.g., with vaporizing dry ice) and airflow velocity measurements.

2. Separating buffering condition from the critical area inside an LAFW

Within the LAFW, a specific section should be designated and demarcated as the critical area within which only critical activities, such as aseptic processes, are performed. The front boundary of this area should be at least six inches from the front edge of the LAFW. The side boundaries should be appropriately placed relative to the number of critical and noncritical functions to be performed inside the LAFW, and the number of articles being used for these tasks. Boundaries should be clearly recognizable, for example, by observable markings.

In vertical LAFWs, tasks and articles involved in aseptic processing should be properly positioned within the demarcated critical area. Some facilities have ensured proper positioning by establishing a perforated platform within the critical area.

In horizontal LAFWs, operations involving aseptic processing should be carried out as close to the airflow source as possible. Operators should wear face masks for breath deflection. Appropriate spatial arrangement of objects and procedures should ensure that the physical or conceptual interface separating the Class 100 area and the buffering conditions is constantly maintained.

The clean air envelope is established by the HEPA-filtered, laminar flowing air in the critical area. A continuous flow of unobstructed air is essential when performing aseptic tasks. Written procedures should be established and followed by operators performing aseptic tasks in the critical area to ensure the clean air envelope is maintained. Room air may not be the only gas in close proximity to the critical area and aseptic operations. Other gases, such as nitrogen or carbon dioxide, which may contact the product, container or closure, or product surfaces (e.g., purging or overlaying) should be appropriately sterile filtered to maintain high particulate and microbial quality. In addition, compressed air should be free from demonstrable oil vapors.

Critical areas should have a positive pressure differential relative to adjacent controlled areas. A pressure differential of 0.05 inches of water is acceptable. Aseptic processing should always be performed in critical areas under a positive airflow pressure. The adjacent controlled area and the rest of the building may have negative airflow pressures. One method for achieving these airflow gradients is to use airlocks or an anteroom between the aseptic processing areas and the rest of the building.

Final container assembly should be performed to totally close the system prior to its removal from the critical area. For example, the steps in such a closed process might include:

a. Connecting a 0.2 μm sterilizing filter to the fluid pathway needle in the final container

b. Attaching a 0.2 μm filter as the vial's air vent needle, if needed

c. Affixing a 0.2 μm filter or a new sterile syringe to a pre-attached sampling port needle

Precautions should be taken to prevent slippage or detachment of components in the aseptically closed final container assemblies from the chemical synthesis apparatus.

The following steps are not considered to be aseptic processes and do not need to be conducted in the critical area:

a. Attaching the distal tubing from the synthesis apparatus to the upstream connector of the sterilizing filter

b. Drawing the postfilling sample from the vial through the filtered sampling port

c. The rapid removal of a needle from the stopper after filling

However, when sampling for sterility testing involves the withdrawal of a drug product from a filled vial, the procedure **should** be performed as an aseptic process in suitably controlled environmental conditions to protect the test sample from potential microbial contamination. (See Sampling in Section X.)

D. Controlled Area (Class 100,000)

The LAFW should be located in a controlled area. Many PET centers can successfully

achieve acceptable air quality in the controlled area without special air handling controls. Air in controlled areas is generally of acceptable particulate quality if it has a per-cubic-foot particle count of not more than 100,000 in the size range of 0.5 micron or larger (Class 100,000) and a microbial count not exceeding 25 colony forming units per 10 cubic feet.

Certain fundamental precautions should be provided and observed to ensure that air quality is acceptable:

1. The LAFW should be situated in the section of the room with the least amount of traffic and activity, preferably at the end opposite the doorway.

2. Aseptic processing tasks should be performed during defined time periods. Ideally, they should be performed when there is a low potential for particulate and bacterial contamination (i.e., during a continuous period of little or no activity within the adjacent controlled area.) Consideration might be given to the preparation of container assemblies at the beginning of the day before other daily activities begin and before additional personnel have entered the room.

3. Surfaces within critical and controlled areas should be constructed of smooth, easily cleanable, nonshedding materials. The controlled area should not be carpeted, or have porous floors, walls or ceiling tiles that cannot be properly cleaned or sanitized. The controlled area also should be free of overhanging pipes or fixtures.

4. All parts of the controlled area should be easily accessible for cleaning and disinfecting. Equipment and furniture used in the controlled area should be constructed of smooth, cleanable, nonshedding materials whenever possible. According to the PET center's written policies and procedures, cleaning and disinfecting surfaces, equipment, and furniture should be accomplished using standard approaches to good housekeeping.

5. The surfaces in all areas should be cleaned and sanitized with suitable frequency by specially trained personnel. Written policies and procedures for cleaning and sanitizing surfaces, equipment, and furniture should be designed to ensure consistent achievement of the intended or specified microbial and particulate quality for that area.

The degree of microbial and particulate control in the controlled area may be less stringent than that for the buffering conditions or the critical areas. However, the extent of cleaning and sanitizing should ensure that the barrier capabilities between the buffering condition and the controlled area are not over

challenged.

6. Activities and functions that are not absolutely necessary or part of the actual processing of PET radiopharmaceutical drug products should not be performed in the controlled area. Unnecessary personnel traffic should be minimized. Particulate-generating activities, such as removal of solutions, drugs, chemicals, and supplies from cardboard boxes should not be performed in the controlled area. Likewise, office supplies and reference books should not be permitted in the controlled area.

In considering what equipment should be located in or what tasks should be performed in the controlled area, an optimal balance between functional necessity versus the contribution as potential sources of contamination should be an essential part of the decision-making process.

7. Personnel entering the various areas or performing particular tasks should wear appropriate protective apparel and follow procedures that are appropriate for the level of cleanliness required for a specific area. Personnel should wear clean clothing covers or clean long-sleeved lab coats that generate low numbers of particles (e.g., material such as Tyvek). Head and facial hair should be covered, and shoe covers worn in the controlled area. Clear gowns or closed coats with sleeves should have elastic bindings at the cuffs. The wearing of jewelry on the hands, fingers, and around the wrist should be minimized or prohibited.

8. The number of personnel in the controlled area at any time should be limited as another measure to promote general cleanliness. Eating, drinking, smoking, and wearing or applying cosmetics should never be permitted in the controlled area.

9. When working in an LAFW cabinet, sterile gloves should be used with cuffs that extend over the lab coat sleeves. Aseptic techniques should be consistently employed. For example, articles should be kept as deep as possible within both the buffering condition and the critical areas. Face masks should always be worn during the performance of aseptic procedures.

10. Written policies and procedures should be established and followed that are appropriate for the intended level of cleanliness of the areas. A specific concern is the proper introduction of articles from one area to an area of higher quality. Only clean, low-shedding or nonshedding articles may be introduced into the buffering condition. The surfaces of non-sterile items should be sanitized with an appropriate disinfectant (e.g., sterile 70% isopropyl alcohol) before being placed in the critical area. Only sanitized or sterile articles

introduced from the buffering condition should be placed in critical areas.

E. Cleaning and Disinfection

General custodial personnel from the medical center or equivalent should be able to perform some cleaning and sanitizing functions for the controlled area. When housekeeping personnel are involved in cleaning the controlled area, they should receive adequate training, follow applicable procedures, and be supervised by trained PET center personnel.

The cleaning, sanitizing, and organizing of the critical area and buffering condition should be the responsibility of trained and supervised PET center personnel who follow appropriate written policies and procedures. Cleaning, sanitizing, and organizing the critical area and the buffering condition should be performed at least twice (i.e., before and after) for each distinct operation or procedure.

Before each distinct operation or procedure, all items should be removed from the critical area. All surfaces of the criteria area should be wiped clean with a freshly prepared mild detergent followed by an approved sanitizing agent. Personnel should allow sufficient time for the sanitizing agent to achieve its antimicrobial effect.

Recleaning should be performed during operations if spillage or other events indicate such a need. It should be realized, however, that recleaning activities may disrupt the atmosphere surrounding the critical area and present a potential for product contamination.

Work surfaces and counter tops near LAFWs in the controlled area should be cleaned in a similar manner. Storage shelving in the controlled area should be emptied of all supplies and then cleaned and sanitized using approved agents with effective frequency. All articles should be cleaned before reshelving.

Cleaning and sanitizing should be sufficiently frequent to ensure the consistent control of environmental quality, as determined through the routine collection of environmental monitoring data. One should not wait until environmental data show that the facility is going or has gone out of control before initiating cleaning or sanitization. See the section on Environmental Monitoring below for further information.

Supplies, equipment, and other articles introduced or brought into the buffering conditions from the controlled area should be wiped with a suitable cleaning agent or removed from their shelf-storage cartons or containers at the interface between the controlled area and the buffering conditions. Subsequently, nonsterile articles should be sanitized with a suitable disinfectant. Sterile articles should be removed from their protective package or wrap (taking care not to open sterile fluid pathways or expose

sterile product contact surfaces) at the interface between the buffering conditions and the critical area.

Cleaning and sanitizing activity in an LAFW should proceed in a direction away from the critical area. Cleaning of the controlled area should begin at the end of the buffering conditions, and proceed in all directions away from the buffering and critical areas. Storage shelving should be emptied of all supplies when cleaned and sanitized, and articles should be cleaned before reshelving. Cleaning and sanitizing should be scheduled and performed by trained and supervised personnel according to written policies and procedures using validated methods.

Only approved cleaning and sanitizing agents should be used. Sanitizing agents should be effective against bacterial spores and a wide variety of microorganisms that are likely to be encountered on the work surfaces. Seventy percent isopropyl or ethyl alcohol that has been filtration sterilized and is checked periodically for evidence of visible contamination can be used. However, seventy percent isopropyl or ethyl alcohols are not the only sanitizing agents that may be used for these purposes. Cleaning and sanitizing agents should be compatible with their surfaces and should not leave unacceptable chemical residues or films.

Wipes should be disposable. All reusable cleaning articles such as sponges and mops should be dedicated for their specific area of use (i.e., inside the critical area (LAFW) or for the controlled area). Wipes and sponges used inside the critical area (LAFW) should be made of nonshedding material. Cleaning materials (e.g., sponges, mops, wipes) used in the controlled area should be constructed of low shedding material. Reusable cleaning materials (such as mops and sponges) should be properly cleaned, rinsed, and, where indicated, sterilized prior to their reuse according to written policies and procedures using validated methods.

F. Equipment Testing

The routine and regular integrity testing of the LAFWs HEPA filters is essential to ensure that the environmental quality of the critical area is maintained. Integrity testing of HEPA filters (e.g., DOP challenge tests) is used to detect leaks around the sealing gaskets, through frames, or through the filter medium. Certification of the LAFW should be performed by a qualified contractor when the unit is initially installed, if it is moved and at suitable intervals, typically every six months. More frequent testing may be necessary when air quality is found to be unacceptable, as part of an investigation into a finding of nonsterility in a drug product, or when significant leakage or other defects are detected at the 6-month interval. The prefilters in the LAFW should be changed periodically according to written policies and procedures by qualified PET center personnel.

The laminar airflow velocities should be monitored regularly at the work surface as well as at the HEPA filter face to ensure adequate uniformity throughout the critical area. Equipment problems can alter airflow velocity. Significant imbalances or reductions in airflow velocity can occur that alter or even extinguish the laminar flow of air to an extent that adequate protection of the critical area is lost. The operator may not be aware of such malfunctions or inadequate conditions. Because the instrumentation and techniques for monitoring airflow velocity are relatively inexpensive, simple, and quick, at least monthly checks of airflow velocity by PET center personnel are highly recommended.

It is essential to maintain appropriate air quality and flow, which can be easily disrupted or influenced by structure, objects, and configuration of equipment and articles within the critical area. Disruptions or influences on air quality and flow can cause undesirable stagnant air pockets, eddy currents, and backwash of potentially contaminated air into the critical area. These disruptions or influences on airflow should be evaluated by assessing to ensure that Class 100 conditions are maintained.

One simple and acceptable approach for observing airflow patterns uses visible carbon dioxide vapors from dry ice placed in the proximal airstream. The visible CO_2 stream can demonstrate influences on or disruptions in airflow around objects and past surfaces. An acceptable configuration for airflow within the critical area should help ensure that Class 100 conditions are maintained. Established configurations of equipment and operations should be followed. If changes occur in equipment configuration, operations, or workflow, reevaluation of airflow patterns within the critical area should be performed.

G. Environmental Monitoring

The classification of controlled environments is based upon the measurement of total nonviable particle counts (see the Federal Standard 209E Clean Room and Work Station Requirements for controlled environments). Particulate monitoring should be performed at least daily under dynamic conditions in the presence of actual production equipment with the configuration of personnel present and during actual production activities. It is essential to ensure that Class 100 conditions are being maintained in the critical area, and that the buffering conditions are maintained, preferably at least at Class 10,000 conditions.

Particulate monitoring is usually performed with electronic instruments displaying immediate results that relate particle size and counts, volume of air, and sampling time and duration. Different types of instruments are available. Measurements can be made as needed, or, with most instruments, automatically obtained on a planned, ongoing schedule. Instantaneous availability of results permits real-time assessment of environmental particulates and permits rapid adjustments in the control program. It

should be noted, however, that particulate monitoring does not distinguish between viable and nonviable particulates.

In aseptic processing, one of the most important controls is the establishment of an appropriate environmental monitoring program. The facility should be monitored in a manner adequate to demonstrate that the intended environmental conditions are consistently maintained and to warn when environmental quality is going or has gone out of control. An environmental monitoring program for PET centers should include, at a minimum, the microbial sampling of surfaces and personnel, the monitoring of observable personnel performance during the manufacturing process and when performing aseptic techniques, and the monitoring of the facility's overall environmental control policies and procedures.

Surface monitoring procedures should be adequate to ensure consistent, effective disinfection and to ensure compliance with proper techniques to avoid recontamination. Daily or lot-by-lot surface sampling in the critical area and the buffering conditions should be performed. Contact (e.g., Rodac) plates or swab-rinse techniques are usually acceptable methods. However, the appropriateness and acceptability of these methods will depend upon the location and intended use of the surface sampled.

Contact plates should not be used on surfaces where complete removal of any residual agar cannot be fully ensured. Fluids used for the swab rinse procedure should not inhibit microbial growth. A combination of sampling sites and scheduling of samples should be representative of the greatest number and the widest range of microorganisms that are most likely to accumulate in the facility.

Written procedures should ensure that personnel are continuously monitored throughout the manufacturing process to ensure that proper gloving, gowning, glove sanitization, and touch control techniques are performed. A standard touch-plate method can be used by pressing the forefinger tips and thumb tips of the gloved hands against an agar surface using a consistent firmness.

As part of an operator's initial gloving qualification, touch-plate fingertip testing should be performed and certified free of microbes at the conclusion of the gloving procedure. After initial qualification, daily postprocessing fingertip, touch-plate testing should be performed during routine production operations. This type of daily testing should be continued until the operator’s use of proper techniques has been established as evidenced by consistently low fingertip contamination. All qualification and testing methods should be established in and performed according to the PET center's written policies and procedures.

It should be noted that the complete absence of microorganisms on fingertips is not a realistic expectation during routine production. Operators are handling sanitized but

not sterilized surfaces during their aseptic manipulations.

Microbial monitoring has its greatest value when recoveries show trends (consistent or otherwise) or acute out-of-limit observations. The monitoring data should be regularly reviewed as part of the current critical evaluation. When any abnormal trends or out-of-limit observations occur, an investigation should be conducted promptly and should include the following:

1. Identify (by at least genus) the organism in a positive sterility test
2. Review the laboratory's record of tests over time
3. Monitor production area environments
4. Determine the product's presterilization bioburden
5. Review batch production records

Some possible causes for abnormal trends can include:

1. Established or developing unacceptable environmental conditions
2. Poor personnel practices
3. Microbial resistance to disinfectants
4. Inadequate cleaning and disinfectant schedules

At a minimum, PET centers should have an aseptic technique monitoring program for personnel. All operators who perform aseptic manipulations under laminar airflow should accomplish these techniques in a proper and consistent manner, as described in the PET center's written procedures. For example, an evaluation of operator performance of aseptic technique should highlight: (1) Avoiding touch contamination and blockage between the source of the laminar airflow and the critical area; (2) disinfection of areas and work preparation; (3) arrangement of supplies in the work areas and work flow; and (4) sanitization of gloves and articles to be introduced into the buffering conditions and the critical area. The performance of each operator should be repeatedly and objectively evaluated at meaningful time intervals.

Personnel should be trained to detect and correct procedural flaws that might develop. The key is to have a training and evaluation program that prevents, rather than corrects, entrenched problems. Supervisory personnel should be capable of performing

objective evaluations of aseptic techniques based on direct observations and their knowledge of the proper aseptic techniques.

Environmental monitoring also includes evaluating air quality. The literature documents many instances of product contamination caused by bacterial aerosols. Contaminated products have led to outbreaks of bacterial-associated illness and, in some instances, human disability or death. Contamination may also introduce allergens and pyrogens, reduce drug potency, or promote the formation of toxic substances. Such changes could result in the recall, reprocessing, or destruction of the finished pharmaceutical.

Various types of air samplers are available for monitoring the environment and may include liquid impingers, agar impactors, filtration, settling plates, centrifugation, and electrostatic and thermal precipitators. The selection of a sampler or combination of these depends on the special needs of the user, but should contain both active as well as passive sampling techniques. At a minimum, air sampling should occur at least once during each manufacturing cycle. Ideally, air sampling to measure environmental air quality should be performed before the production cycle begins, on initiation, in the middle, and at the end of the manufacturing process.

A written environmental monitoring program should have a scientifically sound sampling schedule, including sampling locations and frequency. In addition, maximum microbial limits should be established along with a definitive course of action to be taken in the event samples are found to exceed established limits. In general, these specified limits should represent conservative values intended to signal potential or actual drifts from the designated levels of quality. These specific limits are commonly referred to as *alert* and *action* limits. In the written environmental monitoring program, there should be an appropriate plan of action that will be initiated whenever the alert and action limits are exceeded.

H. Building Cleanliness and Sanitation

Some PET centers are located in hospitals or medical centers where routine housekeeping for the building proper would be expected to ensure a level of general cleanliness and sanitation suitable for patient care and clinical functions. Such standards are generally adequate to insure cleanliness for the non-controlled areas.

When institutional personnel normally not assigned to the PET center are involved in the cleaning or maintenance within the controlled area, they should receive adequate training on applicable procedures and be supervised by trained PET personnel.

V. EQUIPMENT

A. Regulatory Requirements

21 CFR 211.65 requires, in part, that equipment be constructed so that surfaces that contact components, in-process materials, or drug products are not reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

21 CFR 211.67 requires, in part, that equipment be cleaned, maintained, and sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond its established requirements.

21 CFR 211.68 requires, in part, that automatic, mechanical, electronic, or computer equipment be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance.

B. Target Container and Tubing System

All PET centers should demonstrate and document that the entire manufacturing process used to produce a PET radiopharmaceutical drug product does not alter the product or render it unsuitable for use as the result of contacts with fluid pathways, inner surfaces of vessels, or other product contact surfaces used in the manufacturing processes. PET centers should have data demonstrating the suitability of their manufacturing processes readily available for review and inspectional purposes.

For example, a PET center should be able to document that the particle bombardment process produces an appropriate and consistent effect on the target material. Consideration should be given to any alternation or impurity that might result from target bombardment such as pitting or leaching of the target. Data should document that no such alternations or impurities occur that might adversely affect the target material or the desired radioactive postbombardment substance (radionuclide).

Tubing, valves, chambers, columns, and other related attachments may comprise the various fluid pathways, reaction chambers, portals, etc. in manufacturing processes. All materials used for the entire manufacturing process, including the chemical synthesis (from the particle accelerator-target bombardment to final filtration) should be compatible with the in-process materials and the desired PET radiopharmaceutical drug produced. These materials should not absorb in-process materials, and not leach unintended substances into in-process materials or the finished drug product.

The PET center should have evidence (data) available documenting the compatibilities of all systems and should be knowledgeable of these systems to ensure that only

compatible materials and components are being used in each manufacturing process. Material and component compatibility may also be demonstrated and documented by means other than in-house testing where appropriate.

PET centers should also have adequate documentation available (data) to ensure that all equipment and systems are suitable for their entire duration of use and for the maximum number of lots for which they will be used before replacement. Consideration should be directed to, but not limited to factors such as physical-chemical compatibility, adsorption, leaching, integrity, bioburdens, and pyrogen control. Effects such as aging (stress cracking and brittleness) and the radiation effects on polymer materials should also be included as part of the documented evaluation of materials-systems compatibility.

C. Pyrogen (Endotoxin) Control

The introduction and growth of pyrogen-generating microorganisms within the system should be prevented during the entire manufacturing process. To achieve this, the system should be pyrogen free at the outset. The tubing system should not become a pyrogen source. Daily or lot-by-lot replacement of pyrogen-free tubing is recommended whenever feasible. Where not feasible, a closed system should be maintained that ensures the system is dry during substantial downtime periods.

A closed, dry system may be facilitated by flowing sterile filtered dry gas (air or nitrogen) through the system following the manufacture of a lot. The system can be closed by attaching bacterial filters or reservoirs (e.g., syringes) at each portal with daily replacement, or by limiting entries into the system through syringe-needle penetration of swabbed gum rubber ports. Any procedures requiring the opening of such a system (e.g., to connect transfer devices or other articles to an open portal) should be performed as quickly as possible. Such manipulations may be performed in the controlled area, providing the environmental conditions are suitably controlled.

There may be some systems or parts of the manufacturing system (purification cartridges or syringes of [^{18}O] enriched water) that cannot be dried or replaced on a lot-by-lot basis. In such cases, there should be validated procedures for daily sanitization as an acceptable alternative method to achieve adequate pyrogen control.

The duration of use and frequency of replacement for tubing and related manufacturing equipment should be validated to ensure adequate endotoxin control for the specified time period and under *worst case* operating conditions.

Some phases of the synthesis process may inherently destroy pyrogens. For example, the addition of a strong oxidizing reagent and the application of high heat in the synthesis of [^{18}F] FDG Injection has the potential for pyrogen destruction. It is

essential to document and to validate any step claiming to promote pyrogen destruction. The successful demonstration of a minimum three-log reduction to suitable endotoxin challenge usually constitutes acceptable evidence of adequate pyrogen destruction.

Predetermined action levels of endotoxin (i.e., lower than the specified release levels) should be established. When this action level is exceeded, prompt follow-up should include:

1. Replacement of all components in the manufacturing system before production of the next lot.

2. A thorough investigation of potential sources of pyrogens with correction action as necessary.

3. Appropriate reduction of the timing between replacement of manufacturing components until there is adequate evidence to ensure pyrogens are adequately controlled. If consistent endotoxin control cannot be demonstrated with extended-use components, then extended-use components should not be used in the manufacturing process.

FDA's "Guideline for Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices" (12/87) provides guidance on how to determine endotoxin limits. Endotoxin limits associated with the production of PET radiopharmaceuticals should be based on the assumption that the entire volume of an anticipated lot could potentially be administered to a single patient.

D. Particle Accelerator

The particle accelerator (a cyclotron or linear accelerator) is generally the initial component in the manufacturing process for PET radiopharmaceuticals. Several parameters define the appropriate operation of the particle accelerator. These operating parameters directly influence the potency, purity, quality, and characteristics of the radioactive postbombardment substance (radionuclide) produced for incorporation into the designated PET product.

The particle accelerator production methods and operating parameters should be adequately specified and appropriately validated. Written policies and procedures to document the function and the operation of the particle accelerator should ensure that all intended operating parameters will be followed. Most target materials, like [^{18}O] enriched water, are not generally manufactured in PET centers. Therefore, it is essential that the PET center verify the quality of the target materials.

For each lot of PET radiopharmaceuticals, the batch production and control records should document and verify that all operating parameters as specified in the master production and control records were followed. The limits for the operating parameters should not be exceeded as these parameters directly determine the quality and quantity of the radionuclide produced.

Parameters for the production of radionuclides may include, but are not limited to the following: maximum particle energy, beam current, threshold energy, energy of incident particles, duration of irradiation, proper alignment of the target, isotopic composition of target material, foil window composition ([^{48}V] impurity from irradiation on titanium foils), and the chemical purity of the target material.

PET centers should ensure that the functions and operations of instrumentation, apparatus, recording devices, and equipment that determine, affect, or measure all parameters are routinely calibrated, inspected, and checked. The schedule, extent of calibration, and inspection should be based on the equipment's installation, operational, and performance qualification characteristics. Specified functions and operations involving the particle accelerator or other equipment or instrumentation may be performed under service contracts. The schedule and calibration methods should be explained in the written procedures, and records should be available for inspection at the PET center.

FDA acknowledges that the particle accelerator's output may be adequate for the chemical synthesis of PET radiopharmaceuticals although its actual yield deviates appreciably from theoretical yields (see Section XIII). Some limited flexibility in particle accelerator-operating settings may be necessary to achieve clinically useful quantities of a finished drug product.

In some cases, certain production decisions may be made during the manufacturing of a lot of PET radiopharmaceutical (in the absence of specific written parameters detailing those decisions). When such ad hoc production decisions are made, they should be recorded and documented by designated personnel who are fully qualified by training and experience for certain technical judgments. Such changes should be documented and justified in the batch production and control record.

It is essential to ensure that only properly designated, fully qualified personnel control or make changes affecting the operation of the particle accelerator. Any computerized control programs governing the operation of the particle accelerator should have lockout capabilities within the software program. Effective physical lockouts to the computer controls or other appropriate mechanisms are also acceptable.

E. Synthesis

Synthesis encompasses the entire manufacturing process, consisting of numerous complex, interrelated steps including the addition of reagents, heating, drying, separation, rinsing, elution, chemical reaction, and related processes requiring close control. Generally, the synthesis process may be executed under automated or computer control.

Virtually every step in the manufacturing process is critical in that any deviation exceeding specified limits can potentially result in the finished PET radiopharmaceutical product failing to meet one or more of its quality specifications. The PET center's personnel are responsible for ensuring that the synthesis operation is capable of consistently and effectively meeting its predetermined specifications and that the manufacturing process is operated in a controlled manner.

The manufacturing process should be fully validated based on its operational specifications to produce a uniform product on a consistent basis without regard for an individual drug's release specifications. Validation ensures that all preestablished specifications for the drug's production are consistent with the specifications set out in the approved new drug application, drug master file, or master production and control record.

The entire manufacturing process should be preestablished and fully described in the master and batch production and control records. These records should identify the equipment and instrumentation that will be used in a specified and controlled manner as part of the approved synthesis process. Records should also ensure that all the necessary equipment is operational prior to the preparation of each lot. The daily manufacturing process should be a planned series of specified steps performed according to and verified in the written batch production and control records.

Equipment or instrumentation used in the manufacturing process may be subject to unanticipated problems or malfunction. PET centers should establish and maintain appropriate systems to monitor and to alert production personnel to malfunctions encountered during the drug manufacturing process. Should malfunctions occur, the cause(s) should be identified and any corrective interventions employed. PET centers should ensure that all operations and functions, instruments, apparatus, recording devices, and equipment that determine, affect, or measure control parameters are routinely calibrated, inspected, and checked on a predetermined frequency established in a written program based on their installation, operational, and performance qualification characteristics. All control systems should be verified for functionality and reliability.

F. Computer Control of Equipment

FDA's "Guide to Inspection of Computerized Systems in Drug Processing" (February 1983) and the "Guideline on General Principles of Process Validation" (May 1987) provide information useful to PET centers on designing, installing, validating, evaluating, operating, and controlling the automated, computerized and remote systems useful in the production of PET radiopharmaceuticals.

VI. COMPONENTS, CONTAINERS, AND CLOSURES

A. Regulatory Requirements

Subpart E in 21 CFR 211 (21 CFR 211.80 to 211.94) lists the requirements intended to ensure that components, containers, and closures:

1. Are suitable for use

2. Meet all necessary specifications at the time of use

3. Are adequately protected to avoid contamination, and

4. Do not impart impurities or other undesirable attributes into in-process materials. However, routine production and control procedures listed in Subpart E may not be specifically designed to remove or detect contaminants, impurities or other undesirable attributes in components, containers and closures

The requirements in Subpart E are further intended to prevent mixups and the accidental use of unapproved, unacceptable, or rejected components. Provisions of Subpart E cover the receipt, storage, handling, testing, approval or rejection, and disposition of components, containers, and closures. The record keeping requirements in Subpart E address courses of use for components, containers, and closures. It is essential to ensure the traceability of the component parts contained in the finished drug products as there may be questions, concerns, or recalls of the component parts at some later point in time.

B. Guidance

PET centers are expected to adhere to the requirements for component, container, and closure acceptance and use. There should be detailed written procedures to address the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures. Components, containers, and closures should be handled and stored in a manner designed to prevent contamination.

Bagged or boxed components of drug product containers, or closures should be stored off the floor and suitably spaced to permit cleaning and inspection. Each lot of components, containers, or closures should be identified with a distinctive code. These codes should be used in recording the disposition of each lot. Each lot should be appropriately identified as to its status (i.e., quarantined, approved, or rejected).

Some examples of generally acceptable approaches to compliance, subject to confirmation of facility-specific appropriateness by FDA, are discussed below.

C. Coding, Identification, and Retesting

The manufacturer's (vendor's) immediate labeling plus a simple receiving log may suffice as the coding necessary for tracking control under 21 CFR 211.80(d) for finished articles and for hand-held-sized containers of bulk chemical substances. An appropriate identification as to status (i.e., quarantined, approved, or rejected) should be clearly marked on each item (e.g., bulk substance containers, shelf-pack of vials).

Retesting as described in 21 CFR 211.87 is not generally expected for finished articles that are used within their labeled expiration dating period and that have been stored as specified in their labeling. In such circumstances, adherence to the following procedural controls would be generally acceptable to comply with this section:

1. Stock containers are dated upon receipt.

2. Stock containers are tight and stored under proper environmental conditions, including temperature and humidity control and cleanliness.

3. Stock containers are opened and contents withdrawn under strictly controlled cleanliness of the immediate environment, utensils, and technique.

4. At the time of each use, the contents of stock containers are inspected for visual or other physical evidence of deterioration or other indication of unacceptable quality.

5. The contents of stock containers are used within a reasonable, not prolonged, period of time, as would be suitable in accordance with the stability characteristics of each particular component. The latter can be controlled by a system for writing appropriate dates on the label of each stock container.

Lot-by-lot retesting of [^{18}O] enriched water would not usually be expected if the longest intended or expected length of time of use of [^{18}O] enriched water is validated through appropriate testing in accordance with the methods stated in the approved DMF or NDA. Until consistency is achieved, each lot should be retested at the time of its last

use. Once consistency has been established, it may be acceptable to progressively reduce the frequency of retesting. However, lot-by-lot retesting should resume whenever there is a change in the supplier of [^{18}O] enriched water, or there is evidence of sufficient variability in the quality of a lot of [^{18}O] enriched water over time or the between-lot quality to warrant more intensive testing.

D. Finished Articles Used as Components or Container-Closure Systems

There may be some inherent limitations due to radiation safety considerations in the ability to visually inspect finished PET radiopharmaceuticals drug products. One acceptable approach for some PET radiopharmaceuticals ([^{15} O] or [^{11} C] compounds) might incorporate procedures to provide that: (1) Each component or container-closure system is inspected individually for visual evidence of particulate, foreign matter, and container-closure defects immediately before use; (2) defective components will not be used; and, (3) the batch production and control record of the PET radiopharmaceutical includes a signed or initialed verification that such inspection was conducted and that only acceptable finished articles were used.

E. Analytical and Identity Testing of Chemical Components

21 CFR 211.84 requires that each lot of critical components released for use meet all acceptance specifications for identity, potency, purity, and quality as specified in a drug application, DMF, and the master production and control records. These requirements are essential to the proper synthesis of the active ingredient as well as substances included in the finished product. The chemical, physical, and microbiological stability of the finished drug product, as well as components used to manufacture the product should be tested and documented.

If the initial acceptability of components is based solely on the data in supplier certificates of analysis (COA), 21 CFR 211.84(d) requires drug manufacturers to have suitable evidence establishing the consistent reliability of the supplier's analyses and to conduct at least one approved identity test per lot.

In PET drug manufacturing or when no compendial or approved identity test is specified for a specific component, a reaction-based testing procedure may be established, rather than instrumental testing. Such procedures would capitalize on the fact that if the wrong ingredients are used in the synthesis of the PET radiopharmaceutical, the intended step will not transpire and/or the finished product will not meet its specifications. For example, the method for confirming the identity of [^{18}O] enriched water might involve the testing of the [^{18}F]-Fluoride resulting from its bombardment.

F. Endotoxin Testing of Components

In conventional drug product manufacturing, the requirements of 21 CFR 211.84 states that each lot of each component should be tested to ensure that no lot of any component exceeds specified endotoxin limits. This approach assesses the amount of potential endotoxin that might be carried over to the finished drug product. It is acceptable to establish limits on the basis of tolerable potential carry-over quantities of endotoxin to the finished product. Acceptable means for endotoxin determination include certificates of analyses (COA), contract testing, and in-house testing.

It may be possible to forego endotoxin testing of components when endotoxins are removed by a validated process, such as endotoxin filtration, or when a valid endotoxin test cannot be established. Documented evidence for certain components that establish their inherent inability to support pyrogens may also eliminate the need for component testing for this attribute.

The synthesis processes for PET radiopharmaceuticals may be truly destructive to endotoxin (e.g., prolonged heating of an in-process fluid in strong acid or alkali). Endotoxin testing of any component entering the manufacturing process in advance of the endotoxin-destructive step may not be needed. Some synthesis processes having the capacity to destroy endotoxins should be documented and validated for each step in the manufacturing process. Endotoxin control as part of the synthesis process is discussed under Pyrogen (endotoxin) control in Section V on Equipment.

VII. PRODUCTION AND PROCESS CONTROLS

A. Regulatory Requirements

21 CFR 211.110 requires, in part, sampling and testing of in-process materials and drug products to ensure batch uniformity and integrity.

21 CFR 211.113 requires, in part, the establishment of and adherence to appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile. Such procedures should include validation of any sterilization process.

B. In-Process Sampling and Testing

FDA acknowledges that the sampling or testing of in-process materials may not be appropriate for PET radiopharmaceutical drug products due to radiation safety concerns, the short half-lives of positron emitting radionuclides, the synthesis apparatus, or a combination of these or other factors. Although it is important to

ensure in-process batch uniformity and integrity, alternative means may be considered for in-process sampling and testing. The intended purposes of in-process sampling and testing should be achieved, all equipment controlled and monitored, and parameters validated in the established manufacturing process that demonstrates and documents that the product has acceptable product release specifications.

Methods for in-process testing should be established in the master production and control records and documented in the batch production and control records. Checks and documentation can be manually performed, computer controlled, automated, or employ a combination of these processes. FDA's "Guide to Inspection of Computerized Systems in Drug Processing" (February 1983) and the "Guideline on General Principles of Process Validation" (May 1987) provide information that may be useful to PET centers for the design, installation, validation, evaluation, operation, and control of automated and remote systems used for process control.

C. Sterilizing Filtration

The sterilizing filtration process used in the manufacture of PET radiopharmaceuticals should be fully validated and controlled to ensure the sterility of the finished products on a consistent basis. The validation of a sterilization process involves planned testing designed to demonstrate that microorganisms will be effectively destroyed. All sterilization processes should be specified. Sterilization processes may include, for example, autoclaving to destroy and filtration to remove microorganisms. Once a method has been appropriately validated, these sterilization processes should be performed in a documented manner according to the control parameters in the written procedures.

Sterilizing by filtration should be capable of removing microorganisms from PET radiopharmaceuticals. It is generally accepted that a sterilizing filter is one that, when challenged with the microorganism *Pseudomonas diminuta* at a minimum concentration of 10^7 organisms per cm^2 of filter surface, will produce a sterile effluent. It is also generally recognized that a membrane filter having a nominal pore size rating of 0.2 μm or smaller is consistently capable of meeting this criteria for mobile aqueous liquids similar to PET radiopharmaceuticals. Therefore, a PET center can use a 0.2 μm membrane filter as a sterilizing filter for production. Generally, PET centers employ commercially available, sterile, preassembled, ready-to-use small (e.g., 25 mm diameter or smaller) filtration devices (ready-to-use filter devices) for product sterilization.

Before a PET radiopharmaceutical may be administered to patients, any filtration device used in its manufacture should have been shown to be:

1. Compatible with the product

2. Sized and suitably constructed for the intended filtration time, processing pressures, and associated use of the apparatus

3. Proven effective in sterilizing under the specified operating conditions for its use

Vendor certification of compatibility, suitability, and validation is acceptable.

Manufacturing process parameters including the filtration rate, pressure and duration, temperature, pH, viscosity, ionic strength, and osmolarity, may affect the effectiveness and integrity of filtration systems. Such factors may physically or chemically alter filter integrity, affect microbial capture mechanisms, or shrink the microorganisms. Hydrostatic shock and other system stresses should be taken into account during validation and controlled accordingly during processing.

Validation for the sterilizing process should be all inclusive (worst case situations) based on the specified limits for the product's characteristics, process parameters, and sterilization conditions that may affect the effectiveness and integrity of the filtration system.

After validation, the relationship between filtration effectiveness and specified processing parameters and conditions may be relied on. However, adequate process controls should be present in the manufacturing process to ensure that the validation limits are not exceeded during production.

Lot-by-lot integrity testing should be performed to ensure that the validated filtration device has performed acceptably during manufacture. For small-volume filtration using small ready-to-use devices, it may be acceptable to limit integrity testing to post-filtration. Acceptable test methods for quantitating filter integrity include bubble point, diffusing pressure-hold and forward-flow technologies.

D. Aseptic Processes

All aseptic processes should be validated before PET radiopharmaceuticals are manufactured and distributed. Examples of aseptic processes in the manufacture of PET radiopharmaceuticals include the assembly of the container-closure system, container-to-container transfers with a needle and syringe, and repackaging from a multidose vial into unit-dose syringes. Validation studies should be designed and conducted to document that sterile articles remain consistently uncontaminated during aseptic processing.

The media fill simulation technique involving the use of nutrient growth medium

during a simulated sterile product filling is a well-established approach in the validation of aseptic processing in pharmaceutical manufacturing. This is commonly referred to as *sterile media fills*.

The culture medium used in these media fill simulations should be capable of promoting the growth of a broad spectrum of microorganisms likely to be encountered as production-associated contaminants in the PET center. Commercially available sterile culture media, such as trypticase soy broth, suitably packaged for the PET center's validation requirements, may be used. A PET center may also use culture media prepared and sterilized in-house from reconstituted, commercially available powdered concentrates. In either case, growth promotion should be verified and documented for any media used.

USP methodology for growth promotion is generally acceptable for this testing. Incubation of medium-filled units for a minimum of 14 days, with the first 7 days at room temperature (20-25ºC) and the final 7 days at 30-35°C is an acceptable methodology. The suitability of alternative incubation schedules should be scientifically justified by the PET center to ensure visibly detectable growth of any potentially contaminating microorganisms.

At least three consecutive, successful validation runs (no growth detected) should be performed before an aseptic process can be considered valid. All personnel should therefore perform at least three consecutive successful media fills for any unique aseptic operation. Similarly, at least three consecutive successful media fills should be performed for any operational or configurational change that might potentially contribute to microbial contamination during the aseptic process.

Any sterile media fill failure should be investigated promptly, including identification of the contaminating microorganism(s). At a minimum, this investigation should include:

1. The review of environmental monitoring data
2. The review of personnel practices
3. The review of their aseptic technique
4. The review of the production and environmental control procedures
5. The review of the cleaning, sanitizing, and disinfection procedures

Correction of possible causes for the failure of this test should be instituted promptly and should be fully documented.

Any person who fails to perform a media fill test successfully should perform at least three consecutive successful media fills before resuming routine aseptic processing. When a media-fill failure occurs, the PET center should conduct a complete, documented investigation to determine the possible causes and to take the most appropriate corrective actions previously described as soon as possible.

In each calendar quarter, personnel should successfully complete at least one sterile media fill simulation per assigned aseptic operation for continued qualification. The sterile media fill technique is also suitable for the validation of aseptic processing in PET radiopharmaceutical manufacturing. The validation procedure should be representative of routine production under environmental conditions that simulate actual and preferably worst case conditions established as quality limits for production.

To achieve this, the validation procedure could include but not be limited to:

1. Encompassing and approximating as closely as possible all parts, phases, steps, activities, conditions, and characteristics of the routine process where components, fluid pathways, in-process fluids, etc., are expected to remain sterile.

2. Considering all potential sources of microbial contamination during processing.

3. Accounting for all manipulations, handling, environmental conditions, and other factors that might influence the risk of process-associated contamination. The intensity of challenges should be no less than the greatest risk that would be encountered during routine production (e.g., the maximum number of assemblies prepared at one sitting).

4. Imposing the most rigorous challenges to operator technique. This is particularly important in manual aseptic processes, which may be employed in some PET centers. Production personnel should be expected to conduct media fills under the same conditions as those encountered in actual production (i.e., under the same level of fatigue, stress, and pace encountered in the most intense conditions of routine production.)

5. Performance under the conditions of environmental quality equivalent to routine production and preferably including worst case situations.

6. Requiring the processing of no less than the maximum number of units processed during the most intensive production schedule actually employed.

Environmental and personnel monitoring should be performed during the validation

process. The methods used and the quantity of data collected during the validation process should be sufficient to establish appropriate monitoring parameters and limits for routine production.

VIII. PACKAGING AND LABELING CONTROL

A. Regulatory Requirements

21 CFR 211.122 to 211.134 contain numerous requirements intended to ensure that finished drug products are accurately labeled. These requirements deal with the receipt, identification, storage, handling, sampling, examination, and testing of product labeling and packaging materials; labeling issuance; packaging and labeling operations; and drug product inspection. However, the requirements contained in 21 CFR 211.132 for tamper-resistant packaging for over-the-counter (OTC) human drug products are not included in this guidance because PET radiopharmaceuticals are not OTC drugs.

B. Guidance

FDA acknowledges that the ways in which packaging and labeling are accomplished in the manufacture of PET products differ appreciably from these functions in conventional drug pharmaceutical manufacturing. For example:

1. Labels for PET radiopharmaceutical drug products may be printed on the day that the lot is manufactured and in quantities limited to the manufactured lot and its production records.

2. The printed label typically contains lot-specific information entered into the computer at the time of printing, as well as product-specific template information retrieved from a computer file.

3. Printed labels may be manually affixed one by one to each article.

4. Because of radiation safety considerations the immediate product container may have to remain continuously within its lead shielding (commonly referred to as a *pig*) from the end of the synthesis process until such time (i.e., sufficient half-lives) have transpired to allow the safe removal of the vial from the pig. A requirement to affix a label to the immediate product container would not be warranted based on risks associated with possible radiation exposure.

Although the application of specific regulatory requirements for certain aspects of the packaging and labeling of PET products may necessitate some special interpretation,

such operations are still expected to comply with statutory CGMP requirements and the full *intent* of the CGMP regulations.

PET centers are expected to have appropriate written procedures for labeling along with examples of these approaches. Labeling controls should ensure the following:

1. Label contents are accurate.

   a. 21 CFR 211.122(a) requires, in part, that there be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling. For computer-generated labels produced at the time of use, there should be policies and procedures that allow only authorized personnel to generate labels (e.g., the computer may have a lockout system to prevent unauthorized label generation. In addition, labels should be prepared for only one lot at a time and only in quantities sufficient for that lot.)

   NOTE: FDA's "Guide to Inspection of Computerized Systems in Drug Processing" (February 1983) should be consulted for guidance pertaining to computer-generated labels.

   b. 21 CFR 211.122(a) further requires, in part, that those labeling materials should be representatively sampled and examined or tested before use. In addition, 21 CFR 211.125(b) requires that labeling materials issued for a batch should be carefully examined for identity and conformity to the appropriate specified labeling. For computer-generated labels produced at the time of use, both requirements may be met by examining the labels when they are generated to assure their correct identity and conformity. These labels should be compared to the appropriate approved master labeling and should be documented.

2. Each container has the correct label affixed to it.

   Section 211.130 specifies a number of requirements designed to ensure that correct labeling is applied or affixed to each container of drug product. The following special procedure could be used by preparing two types of labels per lot:

   a. Although a complete lot-specific finished product label should be affixed to the pig containing the filled multiple dose vial, an incomplete label may be affixed to the pig prior to the PET product filling the vial. Information such as activity may be written directly onto this label by hand after filling.

b. A lot-identifying pre-label, which may be identical to the incomplete label affixed to the pig, may be affixed to the unfilled multiple dose vial before placing it in the pig.

i. In this circumstance, an incomplete label identical to that affixed to the pig is incorporated into the batch production record. The information necessary for label completion is written simultaneously on the pig label and the label in the production record so that both are identical. If different from the incomplete label affixed to the pig, a duplicate of the lot identifying vial label should also be incorporated into the batch production record.

ii. There is written verification that no old label appears on the pig (which may be reused indefinitely) when the new label is affixed [21 CFR 211.130(e)].

iii. One of the conditions of lot release is that a second person

- verify the accurateness and completeness of the label contents
- verify the placement of the correct label on the corresponding container or pig

Verification should be documented on the production batch and control records.

Such a system conforms to 21 CFR 211.122(g)(3), which describes special control procedures required when cut labeling is used.

Further details concerning regulatory requirements for individuals performing second person verification are contained in 21 CFR 211.25. The second person performing these tasks should have received adequate training to successfully fulfill the task.

Adequate training for such individuals should include the ability to discriminate with 100 percent accuracy between correct and incorrect labeling and the knowledge and ability to take appropriate action in either instance. Where labels are affixed to their respective pigs by a second person, training should also include the ability to discriminate between correct and incorrect containers.

3. Labeling mixups are avoided.

a. The second person should allow no delay between proofreading and affixing the label, and the label should not leave his or her hands between these tasks. This practice should avoid label mixups in situations where the second person affixes labels to their respective pigs after proofreading these labels.

b. Section 211.122(d) includes certain storage requirements for labeling, intended to preclude label mixups. All appropriate measures should be taken to handle labels in a manner that minimizes the risk of mixups with any other labeling materials.

4. Adequate lot-specific packaging and labeling records are maintained as required by regulations.

a. Labeling records must be maintained (e.g., by examining packaging and labeling materials (21 CFR 211.130(d)).

b. The packaging and labeling facilities must be inspected (21 CFR 211.130(e)).

c. Batch production and control records must be maintained (21 CFR 211.188(b)(6) and (b)(8)).

IX. HOLDING AND DISTRIBUTION

A. Regulatory Requirements

Written procedures are required for the warehousing of quarantined drug products, for drug product storage under appropriate conditions, and for distribution [21 CFR 211.142 and 21 CFR 211.150].

B. Guidance

The written procedures specified in 21 CFR 211.142 for warehousing and in 21 CFR 211.150(a) for distribution need to be appropriate for the activities of the PET centers and their manufacture and distribution of PET radiopharmaceutical drug products.

There should be written procedures to ensure that drug products are not distributed before they are released, as required by 21 CFR 211.142(a). These procedures should ensure that the products are held, however briefly, under appropriate conditions that

will not adversely affect them (21 CFR 211.142(b)).

In accordance with 21 CFR 211.150(b), at least a simple distribution log documenting the date and destination of each lot of PET drug product should be maintained and kept current.

X. TESTING AND RELEASE FOR DISTRIBUTION

A. Regulatory Requirements

21 CFR 211.165(a) requires that for each manufactured batch of drug product, there should be appropriate laboratory determinations to establish conformance with that drug product's final specifications prior to release.

21 CFR 211.167(a) requires that for each batch of drug product purporting to be sterile and/or pyrogen-free, there should be appropriate laboratory testing to establish conformance. However, 21 CFR 211.165(a) permits release of specific batches of short-lived radiopharmaceuticals before completion of sterility or pyrogen testing, provided that such testing is completed as soon as possible.

B. Release Testing

Each lot of a PET radiopharmaceutical should be tested and should conform with written, approved test parameters that generally include color, clarity, radiochemical purity, radiochemical identity, specific activity, total activity, radionuclidic purity, radionuclidic identity, chemical purity, and pH. The short half-lives of PET radiopharmaceuticals may preclude the completion of all tests prior to product release. In such circumstances, the sponsor should establish all testing procedures, including methods, specifications, and validation of these methods, in the NDA.

Sterility and/or pyrogen tests should be conducted for injectable PET drug products. However, such injectable PET radiopharmaceutical drug products may be released prior to completion of these tests provided such tests are completed as soon as possible. The sections on Sampling and Sterility Testing Methodology will discuss sterility testing in more detail.

C. Sampling

When a lot or batch of drug product consists of a single container of a PET radiopharmaceutical, approaches that provide a representative sampling of the container's contents can be used. A sampling procedure should not create contamination risks to the remaining contents. For example, the vial stopper of a

finished drug product should not be penetrated with a needle and a syringe unless in an environment that is maintained in Class 100 conditions.

Following are some acceptable approaches for sampling (this is not an exclusive list of examples):

1. A syringe and needle are aseptically attached to the vial as part of the container assembly. After the filled vial is detached from its filling needle, the sample is drawn directly into the syringe. The needle is then quickly removed from the stopper. This final step should be conducted as an aseptic process in the critical area.

The critical area should be maintained in Class 100 conditions (in an LAFW, positive pressure glove box, or other contained atmosphere) and provided an effective airborne microbial control. The exposed needle, once withdrawn from the stopper, creates an opportunity for microbial contamination of the sample. Therefore, an aliquot of the sample should be taken for sterility testing.

2. A 0.2 μm membrane filter and needle could be aseptically attached to the vial as part of the container assembly. After the filled vial is detached from its filling needle, a syringe is directly attached to the filter, and a sample is drawn into the syringe through the filter. Aseptic technique is not required for these steps.

An aliquot from this sampling should be taken for pyrogen testing to ensure that endotoxins are not retained or inactivated by the filter. An aliquot of this sampling should not be taken for sterility testing because of filtering of the sample.

3. After production, the final container could be punctured with a needle and syringe to withdraw the samples. This technique should be conducted as an aseptic process in a Class 100 environment. Furthermore, this aseptic process should be validated to ensure that the remaining contents of the vial do not become contaminated as a result of this invasive procedure.

D. Sterility Testing Methodology

As an alternative to the sampling approaches listed above, the following approach using a proxy container can be used for the sterility testing of single container lots.

For each lot of PET radiopharmaceutical, the production container and a proxy container are aseptically assembled side-by-side. The proxy container should be exposed at the same time and to the same aseptic assembly steps as the production

container. However, the aseptic addition of sterile diluent to the production container is simulated by the aseptic addition of an equivalent volume of sterile Soybean Casein Digest Medium into the proxy container.

Note that the volume of medium added to the proxy container should be appropriate:

- To visualize any subsequent microbial growth
- To prevent interference of growth due to excessive dilution of the sample.

Sterile equipment (filter devices, needles, stoppered vials, airway vent filters) should be used for the proxy sample. Furthermore, the sterile items should come from the same lot used in the manufacture of the companion lot of the PET radiopharmaceutical drug product. The interior of the proxy container is considered to be microbiologically representative of the interior of the production container for purposes of sterility testing.

Aseptic container assembly should be designed to achieve a fluid pathway configuration appropriate for the sterility test sampling procedure. Using a Y-type sterile tubing device, for example, the sterile fluid pathway leading from the sterilizing filter will divide into two branches. One branch leads into the production container and the other into the proxy container. Pinch clamps or equivalents are affixed to each branch for a proper diversion of the sterile fluid. After the production container has been filled with active ingredients, the line to the production container is closed and the line to the proxy container is opened. Caution should be exercised to ensure that undesired fluid does not gain unintentional entry into the production container. The needle should be removed from the production container as soon as this line is clamped.

A volume of fluid equal to the volume in the production container should be advanced through the sterilizing filter and the proxy container as a sterility test sample. It is not necessary for this fluid to contain the PET radiopharmaceutical drug product.

The proxy container should be equipped with a sterile vent filter and incubated at room temperature (20-25^{o}C) in an upright position for a minimum of 14 days. The contents of the proxy container should be observed and results recorded daily for growth. Observations and documentation are not required on nonproduction days or on days when personnel are not normally present in the facility.

The sterility testing procedure used by PET centers should be properly validated to ensure the reliable detection of growth of possible microbiological contamination of PET radiopharmaceuticals.

If the results of any sterility test are positive for microbial growth, a complete investigation should be conducted immediately. Corrective actions based on the results of the investigations should be implemented before further production. For further information on the investigation of sterility test failures, please see FDA's "Guideline on Sterile Drug Products Produced by Aseptic Processing" (June 1987), pp. 36-41.

A sterility test result that is positive for microbial growth is highly suggestive of inadequate operator technique. All aspects of the manufacturing process should be investigated thoroughly. Any operator involved in any aseptic process where a sterility failure is documented should be requalified in each step of the aseptic process (e.g., container assembly, aseptic attachments, content sampling, sterility test sampling). Requalification should occur before any operator is allowed to perform aseptic processes involving the production lots.

XI. STABILITY TESTING AND EXPIRATION DATING

A. Regulatory Requirements

21 CFR 211.166 requires, in part, a written testing program designed to assess the stability characteristics of drug products and the use of such results to determine appropriate storage conditions and expiration dates. This section includes certain requirements for the written program, such as appropriate test intervals and adequate number of test batches. Section 211.137 requires that drug product should bear expiration dates that have been determined by appropriate stability studies.

B. Guidance

For each PET radiopharmaceutical drug product, PET centers should establish minimal standards below which the product would be considered to be unsuitable for use (see Section X on Testing and Release for Distribution for guidance covering content testing).

The stability plan for each PET radiopharmaceutical should incorporate those parameters stated in the approved drug application. In establishing and verifying the real-time stability for a drug product, PET centers should dedicate three initial lots of a PET radiopharmaceutical to this purpose. The expiration date/time assigned to each lot (expressed as the date, the hour, and the minute beyond which the PET radiopharmaceutical cannot be used) should ensure that at least the minimum specified limit for each specified content parameter will be present at that time.

The drug product's stability characteristics should be reflected in the product's labeling. Observed and measured parameters for testing for a drug product’s acceptability, stability and expiration dating are specified in the corresponding approved new drug

application. Further guidance may be found in FDA's "Draft Guideline for Submitting Supporting Chemistry Documentation in Radiopharmaceutical Drug Applications" (November 1991).

Generally, annual stability testing is recognized as good manufacturing practice for conventional drug products, under the provisions of 21 CFR 211.166. This requires the testing of an adequate number of batches to determine an appropriate expiration date. Due to the short life of PET drug products and the nature of radioactive decay, FDA would expect PET centers to revalidate a PET radiopharmaceutical's stability annually, as part of its normal, routine production.

XII. RESERVE SAMPLES

A. Regulatory Requirements

21 CFR 211.170(a) requires the retention of reserve samples representative of each lot in each shipment of each active ingredient. 21 CFR 211.170(b) requires the retention of reserve samples of each lot of drug product. These regulations further specify the quantity, manner, and duration of storage, as well as examination of reserve samples.

B. Guidance

Some PET centers may consider one or more of these reserve sample requirements to be inappropriate or unfeasible due to lot size limitations, to short physical half-lives, radiation safety issues, and the nature of the synthesis process for active ingredients.

When the proposed rule for alternatives and exceptions to CGMP requirements is finalized, PET centers may wish to apply to the Agency for an exception or alternative in accordance with this rule. For example, an exception to the requirement to keep reserve samples for each lot of finished PET drug product might be appropriate when the entire lot consists of only one vial of product.

XIII. YIELDS

A. Regulatory Requirements

21 CFR 211.186(b)(7) requires the inclusion of a statement in master production and control records regarding theoretical production yields and establishing a maximum and a minimum percentage of theoretical production yields). Similarly, 21 CFR 211.188(b)(7) requires the inclusion in batch production and control records of a statement of actual yields and a statement of the percentage of theoretical yields at

appropriate phases of processing. The actual yields and percentages of theoretical yields should be determined at the conclusion of each appropriate manufacturing phase (§ 211.103).

21 CFR 211.101(a) requires that a batch should be formulated with the intent to provide not less than 100 percent of the labeled or established amount of an active ingredient.

21 CFR 211.192 requires a thorough investigation for any unexplained discrepancy noted on review of the batch production and control record. This requirement includes the situation where the actual percentage production yield exceeds the maximum or minimum percentages of a theoretical production yield as established in the master production and control records.

B. Guidance

PET centers should define the acceptable range for the intended (theoretical) yield in their master production and control record prior to the actual manufacturing of a PET radiopharmaceutical drug product.

It is acceptable to have lot-to-lot variation in intended yields within ranges as specified in the master production and control record. With manufacture of each lot, theoretical and actual yields should be compared. If the actual percentage yield falls outside the specified range, an investigation into possible errors or loss of process control should be conducted.

FDA acknowledges that acceptable ranges for theoretical yield for PET drug products may be wider than generally encountered in conventional pharmaceutical manufacturing. However, the specified range should be narrow enough to detect potential manufacturing problems or errors. The acceptability of a range of theoretical yields should be justifiable on the basis of the facility's historical product-specific batch production and control records. This range should be established based on scientific evidence and should never be made on empirical judgments or arbitrarily.

XIV. SECOND-PERSON CHECKS

A. Regulatory Requirements

Several CGMP regulations require a second person to examine, observe, verify, or check various functions (collectively termed *checks*) performed by another person. Such requirements include:

1. Independent checking, dating, and signing by a second person of master production and control records for each drug product [21 CFR 211.186(a)].

2. Independent verification of correct labeling by 100-percent examination for hand-applied cut labeling [21 CFR 211.122(g)(3)].

3. Examining components and verifying their addition to the batch [21 CFR 211.101(c) and (d)].

4. Verifying calculations of yields [21 CFR 211.103].

5. Checking significant manufacturing steps [21 CFR 211.188(b)(11)].

6. Reviewing original laboratory records [21 CFR 211.194 (a)(8)].

7. Double checking the cleaning and maintenance of equipment [21 CFR 211.182].

B. Guidance

Although some PET centers, especially single operator PET facilities, may question their ability to comply with second-person checks, FDA believes these requirements are essential to minimizing the possibility of undetected human error. Therefore, all PET centers are urged to establish a systematic approach for meeting second-person check requirements.

21 CFR 211.25 describes the regulatory requirements for individuals designated to perform second person tasks. 21 CFR 211.25 further requires that each second person should receive adequate training to perform these tasks.

There is a broad pool of potential personnel who can perform second-person checks. In a medical center, it might be feasible to train personnel from other departments to perform these checks on an as-needed basis available to the PET center. The independent checking of master production and control records [21 CFR 211.34] might also be performed by a qualified consultant.

The requirement for second-person verification of hand-applied cut labeling was described in Section VIII, Packaging and Labeling Control. Verification of all checks should be signed or initialed at the time the check actually is performed.

XV. RECORDS AND REPORTS

A. Regulatory Requirements

21 CFR 211.196 requires distribution records to contain certain information about the distribution of drug products.

21 CFR 211.184(c) requires an individual inventory record of each component, drug product container, and closure, and, for each component, a reconciliation of the use of each lot of such component.

B. Guidance

For PET products distributed only to their radiopharmacy or nuclear medicine service in the same medical center, medical complex, hospital, or other clinical building in which the PET center is located, the requirement for distribution records in 21 CFR 211.196 could potentially be achieved with general statements in standard operating procedures identifying the specific drug products and the locations to which those drug products are distributed.

Some PET centers may question the need to meet all of the requirements of 21 CFR 211.184(c) for inventory and reconciliation records of components, containers, and closures used in the finished drug product, as defined in Section VI, Components, Containers, and Closures. PET centers may wish to apply to the Agency for an exception or alternative in accordance with the rule discussed in Section I of this guidance. Such a request might take into account the small quantities involved and the degree to which the information required by 21 CFR 211.184(c) might be readily traceable from other available records including receiving logs and batch records.

XVI. REFERENCES

U.S. Department of Health and Human Services, Food and Drug Administration (FDA). 1983. *Guide to Inspection of Computerized Systems in Drug Processing*. February 1983.

FDA. 1987. *Guideline for Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices*. December 1987.

FDA. 1987. *Guideline on General Principles of Process Validation*. May 1987.

FDA. 1987. *Guideline on Sterile Drug Products Produced by Aseptic Processing*. June 1987.

FDA. 1991. "Draft Guideline for Submitting Supporting Chemistry Documentation in Radiopharmaceutical Drug Applications," FOD Doc. No. 2009. November 1991.

ATTACHMENT A

GLOSSARY OF TERMS

The following terms associated with the manufacture of PET radiopharmaceuticals are used in this guide:

Active ingredient: any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. 2-Deoxy-2-[^{18}F]fluoro-D-glucose ([^{18}F]-FDG) used in the manufacture of FDG Injection is an example of an active ingredient.

Batch: a specific quantity of a drug or other material that is intended to have uniform character and quality, within specific limits, and is produced according to a single manufacturing order during the same cycle of manufacture. In the case of PET radiopharmaceuticals manufacturing, the material produced during a single irradiation cycle using a synthesis and/or purification operation would constitute a batch.

Component: any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.

Controlled environment: an area that provides consistent, specified environmental conditions with defined limits, maintained as limited-access, and providing appropriate environmental monitoring.

Critical area: an area in which sterilized dosage forms, containers, and closures are exposed to the environment, particularly the environment immediately surrounding aseptic-processing activities and critical surfaces.

Critical surface: a surface that comes into contact with sterilized products, sterile containers, or sterile closures.

Drug product: a finished dosage form that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient, but is intended to be used as a placebo.

In-process material: any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product.

Lot: a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits. Or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that ensures it has uniform character and quality within specified limits.

Positron emission tomography (PET): a medical imaging modality used to assess the body's biochemical processes. Radionuclides are manufactured into PET radiopharmaceutical drug products that are then administered to patients for medical imaging. The medical images of the body's biochemical processes are then evaluated, generally, for diagnostic purposes.

PET center: a drug manufacturing facility that produces and distributes PET radiopharmaceuticals. The manufacturing process generally involves the generation of a radioactive postbombardment substance (radionuclide) resulting from the bombardment of a target material by a particle accelerator. The radioactive postbombardment substance is then directly used in chemical synthesis to manufacture a PET drug product under current good manufacturing practices. These PET centers are usually, but not necessarily, located in medical centers or hospitals. The normal daily batch production is usually performed by a multidisciplinary team involving a broad range and level of personnel with appropriate training and experience in radiopharmacy, radiochemistry, nuclear physics, manufacturing and testing of PET radiopharmaceuticals.

PET radiopharmaceutical drug product: a finished radioactive drug product in its final container suitable for distribution. It contains an active ingredient typically in an aqueous system intended for use in PET. The product may or may not include other components, such as sodium chloride for isotonicity or a buffer system for pH control. Fludeoxyglucose F 18 Injection (FDG Injection), Fluorodopa F 18 Injection, and Sodium Fluoride F 18 Injection are examples of liquid injectable PET radiopharmaceuticals.

Positron ($ß^+$): a particle emitted from the nucleus with the same rest mass as an electron but with a positive charge. It is considered to be the antimatter counterpart to the electron.

Positron decay: the emission of positrons from a neutron-deficient and unstable nucleus. The positron has a kinetic energy that carries it through matter. When the positron is almost at rest, it collides with an electron and is annihilated, resulting in the emission of two γ-rays of equal and specific energy (511 keV-equivalent to the rest mass of an electron) in almost exactly opposite directions (180° to conserve near zero momentum). Positron emission effectively creates a neutron from a proton.

Positron-emitting radionuclides: radioactive atoms that decay by partial or total emission of positrons. They are created by the reaction with accelerated particles, produced in a particle accelerator, reactor, or other charge-particle accelerator, on stable target nuclides. [^{18}F]-Fluorine, [^{11}C]-Carbon, [^{13}N]-Nitrogen, and [^{15}O]-Oxygen are examples of positron-emitting radionuclides associated with liquid injectable PET radiopharmaceuticals.

Radioactive postbombardment substance: the material, usually liquid, which contains positron-emitting radionuclides, that is delivered to the reaction apparatus for synthesis of an

active ingredient as an integral part of the manufacture of a PET radiopharmaceutical drug product. [^{18}F]-fluoride or [^{11}C]-labeled precursors for the production of organic [^{18}F] or [^{11}C] active ingredients (e.g., 2-deoxy-2-[^{18}F]fluoro-D-glucose) are examples of these substances.

Target material: a substance in gas, liquid, or solid state to be irradiated by a beam current of charged-particles originated in a cyclotron, or other charge-particle accelerator. It contains the nuclide that will undergo the desired nuclear reaction to yield the positron-emitting radionuclide. [^{18}O] enriched water ([^{18}O]$H_2$0) is an example of a target material; it yields upon bombardment the ^{18}F-fluoride radioactive postbombardment substance used in the manufacture of FDG Injection. Other examples of target materials used for liquid injectable PET radiopharmaceuticals include N_2, Ne, H_2O, N_2(5% H_2), and CH_4. The terms *isotopic composition* and *purity of the target material* refer to the relative percentages of the principal isotope and other isotopes or elements present in the target material. Examples of target material impurities include [^{16}O] residual in [^{18}O] enriched H_2O targets, or traces of Cr, Fe, Co, F, etc., in any water target.

Target unit: the holder containing the target material. Its body is usually built of stainless steel or aluminum with inlet/outlet ports, a surrounding coolant system, and usually a thin foil target window, such as titanium foil.

ATTACHMENT B

Half-Lives of Positron-Emitting Radionuclides Useful or Potentially Useful in PET Radiopharmaceuticals

^{18}Fluorine -- 109.7 minutes
^{11}Carbon -- 20.4 minutes
^{13}Nitrogen -- 9.96 minutes
^{15}Oxygen -- 2.07 minutes